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14. ABSTRACT Breast cancer cells are known to bear determinants that would allow tumor specific immune responses. However, initiation and amplification of such immune responses are critically dependent upon the balance in TH1 and TH2 cytokine profiles. This molecular epidemiological study evaluates the impact that variability in cytokine profiles, (inferred from functional polymorphisms in cytokine genes), may have on breast cancer risk among urban African-American women. In the first phase of the study, DNA collected and approved for additional study as part of a previously funded Case-Control investigation (n=1600) will be assessed for cytokine polymorphisms. Because cytokine profiles are also known to be affected by environmental factors, particularly levels of stress, this study also evaluates the relative contribution of genotype and stress influences using data collected for that purpose from a sub-sample of healthy Controls (n=400) recruited from the "graduates" of the larger study. Results will allow evaluation of the possibility that deficits in cytokine responses due to genetic or environmental factors may contribute to breast cancer risk. Based on these findings, women at risk for breast cancer because of polymorphisms in genes important to effective immune surveillance could be targeted for innovative prevention strategies including stress reduction and immune modulators.					
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**Immune surveillance, cytokines and breast cancer risk:
Genetic and psychological influences in African American women**

Principal Investigator: Dr. Dana H. Bovbjerg

INTRODUCTION:

Ineffective immune surveillance against newly transformed cells may contribute to increased risk of breast cancer. We propose that dysregulation of cytokine production profiles may be one mechanism underlying ineffective surveillance and hence increased breast cancer risk. More specifically, we hypothesize that women whose cytokine responses tend to favor humoral (Type 2) over cell-mediated (Type 1) responses are at risk for developing breast cancer. Because assessments of cytokine responses in blood samples from patients are likely to be affected by the presence of clinical disease and its treatment, this hypothesis can best be tested using a molecular epidemiologic approach. Data suggesting the utility of such an approach to exploring this possible source of breast cancer risk has recently begun to appear in the literature (e.g., Smith et al. 2004). Little is currently known about such effects in African American women. In the context of a previously funded case-control study (n=1600), we can evaluate the role of polymorphisms in cytokine genes associated with dysregulation in relation to breast cancer risk. In a sub-sample of healthy control subjects (n=400), we can also explore the relative contribution of genotype (cytokine polymorphisms) and environmental influences (e.g., stress-induced immune modulation) to cytokine responses.

The study is linked to a project (Ambrosone, PI) approved for funding as part of a Behavioral Center of Excellence award from the Army (DAMD-17-01-1-0334, Bovbjerg, PI). This "parent" project, as well as other related projects, draws on collaborations with physicians at the NYC hospitals that have the largest referral patterns for African-Americans in Manhattan, Bronx, Brooklyn and Queens to recruit newly diagnosed African-American breast cancer patients. Age-matched controls are selected using Random Digit Dialing (RDD). Patients consenting to participate undergo an interview and provide a blood specimen for DNA extraction. For our piggy-backed study, appropriate banked DNA can be genotyped for the cytokine polymorphisms of interest. Additional newly obtained blood specimens from consenting Control participants (n=400) are processed for cytokine responses (phenotype), and an additional set of questionnaires focused on psychological stress is completed at the time of the blood draw. Data analyses will be conducted using standard approaches when required sample sizes are reached.

Concepts from behavioral research and molecular epidemiology are synthesized in this study to address critical questions regarding breast cancer etiology. By exploring hypotheses related to psychoneuroimmunology and using technology and paradigms from molecular epidemiology, this research may make important contributions to identifying causes of breast cancer so that it may be eradicated. By examining case-control differences in cytokine polymorphisms, the role of this aspect of immune function in breast cancer may be elucidated. Furthermore, the evaluation of stress effects on cytokine responses in vitro, particularly in relation to genotype, may provide compelling

support for a possible role of stress in breast cancer etiology.

BODY:

Statement of Work

- Task 0: Successful application for HSRRB approval through USAMRAA office
- Task 1: Setting up study procedures
- Task 2: Inclusion of 1600 Case and Control participants for genotyping
- Task 3: Inclusion of 400 Control participants for phenotyping
- Task 4: Cytokine evaluation of frozen stimulated samples
- Task 5: Analysis of acquired cellular event flow cytometry data
- Task 6: Statistical analysis of cytokine genotype data and preparation of manuscripts
- Task 7: Statistical analysis of cytokine phenotype data and preparation of manuscripts

Approval for the parent project (DAMD-17-01-1-0334, Project 1, PI, Ambrosone) was granted in April 2004, however we did not receive approval for this project until November 2004. In the absence of approval, we spent the first four months of the grant year focusing on tasks 0 and 1. We have trained research assistants and confirmed reliability; we have produced study questionnaires; we have established procedures for coordination with the "parent" project; we have established procedures for coordination with the Recruitment, Tracking, and Interviewing Core of the "parent" Behavioral Center of Excellence (Bovbjerg, PI). With approval now granted, we completed Tasks 0 and 1. Since that time, we have begun Tasks 2 and 3. Progress on these tasks will be facilitated by additional funding received from the NCI (Ambrosone, PI) to expand the case-control study, which should speed the pace of recruitment. We now have access to DNA from 140 Case and Control participants, which can be batch genotyped for the cytokine polymorphisms of interest. We have begun to establish procedures for coordination with the Molecular, Diagnostic and Research Core of the "parent" Behavioral Center of Excellence (Bovbjerg, PI). We have also begun contacting Control participants for inclusion in the phenotyping portion of this study. We have identified 44 potential eligible subjects based on database review. Eleven women were found to be ineligible, or were lost to follow-up. The remaining 33 are in process.

KEY RESEARCH ACOMPLISHMENTS:

At this point in the research, no results are yet available.

REPORTABLE OUTCOMES:

At this point in the research, no reportable outcomes are yet available.

CONCLUSIONS:

If the results of the proposed research are consistent with study hypotheses, the study could have profound implications for the eradication of breast cancer. The results of the proposed research may suggest new means of evaluating genetic risk of breast cancer in healthy women, as well as novel intervention strategies for long term reduction of that

risk, including stress reduction, as well as biological response modifiers designed to ameliorate dysregulation of cytokine profiles.

REFERENCES:

Smith KC, Bateman AC, Fussell HM, Howell WM. Cytokine gene polymorphisms and breast cancer susceptibility and prognosis. Eur J Immunogenet. 2004 Aug;31(4):167-73.

APPENDICES:

N/A